IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Xianghui YI Serial No.: 10/579,288 Filed: May 15, 2006 Title: **DERIVATIVES OF PYRIDONE AND THE USE OF THEM**	Group Art Unit: 1614 Examiner: RAO, Savitha M. Confirmation No.: 7077 Customer No. 21971 **Certificate of Electronic Filing** I hereby certify that this Interview Summary and all attachments are being deposited by Electronic Filing on August 11, 2009 by using the EFS-Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below. By: Christine Nagy Christine Nagy

Mail Stop Amendment
Commissioner For Patents
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Interview Summary

Applicant thanks supervisory patent Examiner Ardin Marschel for taking the time to discuss the Office Action on August 11, 2009. Items discussed during the telephonic interview included the 35 USC §103 claim rejections. Applicant re-explained that the prior art as a whole teaches away from a composition of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone, or other N-(substituted phenyl) pyridone compounds, as demonstrated by the issued claims of European Patent No. 0 702 551, and the Margolin Response dated October 1, 1999 submitted during the prosecution of European Patent No. 0 702 551 (copies of which were previously provided in the Information Disclosure Statement dated September 19, 2007). The Examiner indicated that the response submitted by Applicant dated January 20, 2009 did not provide a copy of the Margolin Response dated October 1, 1999. As requested by the Examiner in order to assist in the consideration of Applicant's arguments, the following documents are provided herewith:

Exhibit A: a copy of the office action dated February 9, 1999 for European Patent No. 0 702 551;

Exhibit B: a copy of the Margolin Response dated October 1, 1999 submitted during prosecution of European Patent No. 0 702 551; and

Exhibit C: a copy of European Patent No. 0 702 551.

Applicant directs the Examiner's attention to the office action dated April 4, 1999 under item 3, last paragraph, where the examiner stated "Unless the applicant can demonstrate a surprising effect, which does not appear from the application as filed, the subject-matter of claim 1-11 also lacks an inventive step." Margolin's surprising effect is that "even minor structural changes from that of pirfenidone can significantly affect the properties as the results presented in the Table will demonstrate." (*see* Margolin response dated October 1, 1999).

The issued claims of European Patent No. 0 702 551 and the statements made by Margolin during the prosecution of European Patent No. 0 702 551 clearly teach away from a composition of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone, or other N-(substituted phenyl) pyridone compounds as instantly claimed. Upon consideration of European Patent No. 0 702 551 and the Margolin Response dated October 1, 1999 in view of Applicant's arguments, Applicant respectfully requests allowance of claims 4-6, 11, 12, 14-19 and 22-29. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
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Date: August 11, 2009

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EXHIBIT A

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Application No	Ref	Date
94 916 710.0-2107	F5086/ISH/MDS	

Applicant
MARGOLIN, Solomon B.

09.02.99

Communication pursuant to Article 96(2) and Rule 51(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(3) and 83(2) and (4) EPC.

Amendments to the description, claims and drawings are to be filed where appropriate within the said period in **three copies** on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

EUROPÄISCHES PATENTAMT - EUROPEAN PATENT OFFICE - OFFICE EUROPÉEN DES BREVETS

LAFFARGUE-HAAK T
Primary Examiner
for the Examining Division

EXRE coded
04.02.99 Bt

Enclosure(s): 2 page/s reasons (Form 2906)

Registered Letter

The examination is being carried out on the **following application documents**:

Text for the Contracting States:
AT BE CH LI DE DK ES FR GB GR IE IT LU NL PT SE

Description, pages:

1-8,12-15,19, 21-23	as originally filed			
9-11,16-18,20	as received on	05.12.1995	with letter of	30.11.1995

Claims, No.:

1-11	as received on	05.12.1995	with letter of	30.11.1995

Drawings, sheets:

1/1	as originally filed

1. Amendments

The amendments (claims and description) submitted by the applicant with a letter dated 30.11.1995 and received 05.12.1995, are allowable with respect to Art. 123(2) EPC.

2. Documents cited

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 : EP-A2-383 591
D2 : US-A-3 974 281 (cited in the application)
D3 : US-A-4 042 699 (cited in the application)

3. Lack of novelty and inventive step (Cl. 1-11)

D1 discloses the use of 5-methyl-1-phenyl-2(1H)-pyridone (=pirfenidone) for the prevention and treatment of fibrotic lesions and anticipates the subject-matter of claims 1-8 and 10-11.

D2 (Ex. 2-30) and D3 (Ex. 3, 4, 6, 7, 12-14) disclose pharmaceutical compositions containing N-substituted 2-(1H) pyridones and therefore anticipate the subject-matter of claim 9. The applicant is reminded that the presently worded claim 9 refers to pharmaceutical compositions per se and not to the use of this composition for treating a particular disease (see also Guidelines C-IV.4.2).

Even if novel subject-matter could be established (e.g. claiming only N-substituted 3-(1H) pyridones), the present application does not meet the requirements of Articles 52(1) and 56 EPC, because the lack of inventive step. The technical problem with respect to D1 (closest prior art), would be to provide substances for treating fibrosis other than N-substituted *2*-(1H) pyridones. As the present invention refers to N-substituted *3*-(1H) pyridones, which are structurally close, it would have been obvious for the skilled person to introduce a minor structural change in order to solve the technical problem. Unless the applicant can demonstrate a surprising effect, which does not appear from the application as filed, the subject-matter of claim 1-11 also lacks an inventive step.

4. Concluding remarks

It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter (e.g. N-substituted *3*-(1H) pyridones) as patentable an independent claim including such matter should be filed taking account of Rule 29(1) EPC.

Tanneke Haak

EXHIBIT B

WITHERS & ROGERS *European & Chartered Patent Attorneys, Trade Mark Attorneys*

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1 October 1999

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Dear Sirs

European Patent Application NO. 94916710.0-2107
Margolin, Solomon B.

We refer to the official letter dated 9th February 1999 and to the extension of the response term dated 21st June 1999 and now file replacement pages 24-26 of the specification containing amended claims 1 to 11 in triplicate. Claims 1 to 9 on file hitherto are now withdrawn.

Further processing is requested in a separate letter of today's date which also authorises deduction of the further processing fee from our deposit account.

The new claims are in second medical indication format and are directed to the use of N-phenyl-2-(1H) and 3-(1H) pyridones in the preparation of a medicament for treatment of fibrotic lesions. The claims specifically exclude the use of 5-methyl-1-phenyl-2-(1H)-pyridone (perfenidone) and are thus believed to define novel subject matter, in that the prior art describes only perfenidone for such use. The right of the applicant to revert to broader claims (still excluding pirfenidone) is hereby reserved.

Although, as explained at length in the description, perfenidone has been shown to have remarkable efficacy in the treatment of conditions involving fibrotic lesions, analogous compounds have now been shown to be superior, either in terms of reduced toxicity, increased activity or both; in any event, they show an enhanced relative safety ratio. Surprisingly and despite the examiner's assertion to the contrary, even minor structural changes from that of perfenidone can significantly affect the properties, as the results presented in the following Table will demonstrate.

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COMPOUND	RELATIVE ANTIFIBROTIC ACTIVITY*	ALBINO MICE I.P., LD_{50}	RELATIVE SAFETY RATIO**
5-methyl-1-phenyl-2-(1H) pyridone (pirfenidone)	1.0	420	1.0
3-methyl-1-phenyl-2-(1H) pyridone	1.0	600	1.4
5-ethyl-1-phenyl-2-(1H) pyridone	8.0	500	9.5
3-ethyl-1-phenyl-2-(1H) pyridone	6.0	600	8.5
5-methyl-1-parahydroxyphenyl-2-(1H) pyridone	0.0	>2000	none

* As measured by inhibition of proliferation and collagen synthesis by graded concentrations of the respective compounds when assayed in standard cultures of human fibroblast cells (WI38).

** relative ratios determined by multiplying values in first two columns, divided by LD_{50} figure for pirfenidone.

It is to be noted that the third and fourth compounds have activities eight and six times greater, respectively, than pirfenidone. Thus a dosage of one-eighth or one-sixth that of pirfenidone provides the same result, while greating lowering the possible toxicity. The last compound, which is not within the scope of the present claims, has no activity.

The present invention provides a very powerful arrest of formation of, as well as causing removal of, pathogenic accumulation of water-insoluble collagenous connective tissue (for example, excessive scar or lesional fibrotic tissue). The powerful pyridones which are the subject of the present claims are effective at as much as eight times lower concentrations than pirfenidone, yet their acute toxicity does not differ significantly from that of pirifenidone. Consequently, not only are these agents more effective, they also afford an unexpected (8 to 10 fold) larger safety margin. The discovery of such greatly increased power for certain compounds is a wholly unexpected finding.

To enlarge on the description at page 19 line 7, idiopathic pulmonary fibrosis (IPF) is a progressive clinical syndrome of unknown etiology and fatal outcome. Currently available therapies are ineffective and associated with significantly adverse effects. Pirfenidone was investigated for its tolerability and usefulness in terminally ill patients with advanced IPF. Consequetive patients with IPF and deterioration despite conventional therapy or who were unable to tolerate or unwilling to try conventional therapy were treated with oral pirfenidone. Treatment was administered on a compassionate basis (open label). Fifty-four patients were followed for mortality, change in lung function, and adverse effects. Their mean age was 62, mean duration of symptoms 4.6 years, and time since lung biopsy was 3.2 years. Conventional therapy was discontinued in 38 of 46 patients; the other eight were able to decrease their prednisone dosage and eight had no previous conventional treatment.

cont...

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One- and two-year survival was 78% (95% CI 55%, 89%) and 63% (95% CI 50%, 76%), respectively. Patients whose lung functions had deteriorated prior to enrolment appeared to stabilise after beginning treatment. Advese effects were relatively minor. Compounds according to the present invention are significantly better than perfenidone and hold out more promise for more effective treatment of IPF.

In the light of the above, it is believed that the invention as now defined in the amended claims is novel and involves an inventive step.

It is required that revision of the description be deferred pending acceptance of the claims.

Oral proceedings are requested as a precaution.

Yours faithfully

I S Harrison
WITHERS & ROGERS
Enc

to examiner
EXH 3
12. 10. 99 IT

EXHIBIT C

(19) Europäisches Patentamt
European Patent Office
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(11) EP 0 702 551 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
25.09.2002 Bulletin 2002/39

(21) Application number: **94916710.0**

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(51) Int Cl.7: **A61K 31/44**, A61K 31/47, A61P 19/04

(86) International application number:
PCT/US94/05156

(87) International publication number:
WO 94/026249 (24.11.1994 Gazette 1994/26)

(54) COMPOSITIONS AND METHODS FOR REPARATION AND PREVENTION OF FIBROTIC LESIONS

ZUSAMMENSETZUNGEN UND VERFAHREN ZUR REPARATUR UND VORBEUGUNG FIBROTISCHER VERLETZUNGEN

COMPOSITIONS ET PROCEDES DE REPARATION ET DE PREVENTION DE LESIONS DU TYPE FIBROSE

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **07.05.1993 US 59214**
19.05.1993 US 64831

(43) Date of publication of application:
27.03.1996 Bulletin 1996/13

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(56) References cited:
EP-A- 0 383 591
US-A- 3 974 281
US-A- 4 042 699
US-A- 5 310 562

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 702 551 B1

Description

Technical Field of the Invention

[0001] The present invention relates to medical compositione and methods for the reparation of fibrotic lesional tissues and the prevention of fibrotic lesions, which compositions comprise one or more N-substituted 2(1H) pyridones and/or one or more N-substituted 3(1H) pyridones as active anti-fibrotic ingredient(s).

Background Art

[0002] Herein, the term "anti-fibro", "anti-fibrotic" or "anti-fibrosis" refers to the reparations and/or prevention of pathological polymerization of collagen in lung fibrosis, arteriosclerosis, prostatic hypertrophy, keloid, myocarditis, collagen disease, scar, wrinkle, etc., and reparation as well normalization of the existing pathological fibrotic tissues.

[0003] Methods of preparation of some N-substituted 2(1-H) pyridones useful in the present invention are described in US Patent No. 3,839,346, issued October 1, 1974, to Gadekar, and titled N-SUBSTITUTED PYRIDONE AND GENERAL METHOD FOR PREPARING PYRIDONES. That patent also describes use of those compounds in analgesic, anti-inflammatory, and antipyretic treatments. US Patents Nos. 3,974,281, issued August 10, 1976; 4,042,699, issued August 16, 1977; and 4,052,509, issued October 4, 1977, all to Gadekar, describe further use of one of these compounds, 5-methyl-1-phenyl-2-(1H) pyridone ("pirfenidone"), in lowering serum uric acid and glucose levels, treating upper respiratory inflammatory conditions, and treating inflammatory skin conditions, in humans and other mammals.

[0004] The use of pirfenidone in the reparation and prevention of fibrotic lesions is described in EP-A-0 383 591.

[0005] It has been discovered by the present inventor that other N-substituted 2(1-H) pyridone compounds and N-substituted 3(1H) pyridone compounds also have anti-fibrotic activity. Heretofore, before the discoveries of the inventions disclosed herein and in the above copending applications, no effective pharmacological agent or composition has been available for the prevention or removal of pathologic fibrotic lesions of the lungs, prostate glands, musculoskeletal diseases, myocardial degeneration, myocardial infarction, arteriosclerosis, and other lesional fibroses.

[0006] For example, powerful anti-inflammatory glucocorticoids (hormones relating to carbohydrate metabolism) such as hydrocortisone or prednisolone administered in very large doses have repeatedly been shown to be ineffective against fibrotic disease. These glucocorticoids do not arrest or remove such life-threatening fibrotic lesions. The glucocorticoids may be effective, however, as anti-inflammatory agents under such condition that they may temporarily ameliorate the secondary acute inflammation flare-ups which intermittently occur in tissues or organs damaged by fibrotic disease. Indeed, excessive and prolonged administration of glucocorticoids in pulmonary fibrotic disease may cause destruction of tissues, due to fibrosis or an exacerbation and acceleration of the fibrotic destruction.

[0007] Antopol (1950) was the first of many investigators who found that the anti-inflammatory glucocorticoids readily enhance fibrotic degeneration of lung tissues. Similarly, the non-steroidal anti-inflammatory agents such as aspirin, salicylates, phenylbutazone, indomethacin, various phenylacetic acid derivatives, and the like have also failed to arrest formation of, or cause repair of progressive, chronic fibrotic damage to lung tissues, prostatic tissues, musculoskeletal tissues, etc.

[0008] Accordingly, it is a principal object of the present invention to provide compositions for the reparation and prevention of fibrotic lesional tissue.

[0009] It is an additional object of the invention to provide such compositions that comprise one or more N-substituted 2-(1H) pyridone(s) and/or N-substituted 3-(1H) pyridone(s) as active anti-fibrotic ingredient(s).

[0010] Other objects of the present invention, as well as particular features and advantages thereof, will be elucidated in, or be apparent from, the following description.

Disclosure of Invention

[0011] The present invention provides the use of a compound selected from 3-methyl-1-phenyl-2-(1H)-pyridone, 6-methyl-1-phenyl-2-(1H) pyridone, 3,6-dimethyl-1-phenyl-2-(1H) pyridone, 5-ethyl-1-phenyl-2-(1H) pyridone, 1-phenyl-2-(1H)-pyridone and 1,3-diphenyl-5-methyl-2-(1H)-pyridone in the preparation of a medicament for the reparation and prevention of fibrotic lesional tissue in a mammal.

Best Mode for Carrying Out the Invention

[0012] The "anti-fibrotic" activity described herein differs from "fibrinolytic" or "anti-fibrin" activity. The fibrinolytic" or "anti-fibrin" activity refers to the biological ability of a pharmaceutical substance to (1) prevent fibrin formation (prevent formation of a blood clot) or (2) lyse or dissolve a previously formed blood clot.

[0013] The "anti-fibrotic" activity discovered by the present inventor and as used herein refers to the ability of an

active substance to (1) prevent an excessive pathologic accumulation of colleagnous scar or connective tissue in various body structures and organs (usually triggered by some injury, allergy, infection, or by some inherited genetic aberration), or (2) cause the non-surgical removal or biological dissolution of an existing excessive and pathologic accumulation of fibrotic collagenous tissue (for example, as in the dissolution of life-threatening fibrotic lesions of the lung found in patients with asbestosis).

A. CONNECTIVE TISSUE PROTEINS OF MAMMALS

[0014] Three major classifications of connective tissue proteins are recognized with the largest portions consisting of collagen types (70 to 80%) and elastin types (15 to 20%). A miscellaneous group constitutes the third and smallest class.

[0015] The general biochemical characteristics of the collagen types which constitute the principal protein (1) in normal white connective tissue and (2) in scar or fibrotic tissue, are summarized in Table 1, as contrasted with elastin types. For example, collagen is sparingly soluble in water, but readily converted to water soluble gelatin upon boiling in an acid or alkali. In contrast, the highly water soluble elastin does not convert to gelatin upon boiling in an acid or alkali.

[0016] The elastin constitutes the principal protein of yellow connective tissue found in elastic structures such as the walls of larger blood vessels and walls of lung alveoli.

[0017] Investigations on the molecular biochemical level of tissues have demonstrated a very slow turnover rate for metabolic processes involving fibrotic lung collagen. In fact, the metabolic rate is measured in years. By contrast, the metabolic rates of the other connective tissue collagens including elastin and the like are measured and expressed in hours and days (White, Handler, and Smith, 1973, page 983).

B. INTERSTITIAL PROLIFERATION (HYPERPLASIA) OF FIBROBLAST-TYPE CELLS IN LUNGS AND OTHER ORGAN TISSUES

[0018] The synthesis of various collagens found in scar or fibrotic structures takes place in fibroblast cells, or fibroblast-like cells, which then extrude the collagen into the surrounding matrix. During this wound repair process, number of fibroblasts at the site, and (2) a sharp rise in the rate of the synthesis and extrusion of collagen. If these two phenomena are not prevented, the pathologic and progressive accumulation of collagen would cause polymerization and fibrotic disease (for example, impairment of respiratory function, impaired circulatory function via fibrotic changes in arterial walls, fibrotic degeneration of renal and liver function, degenerative musculoskeletal function, fibrotic degeneration of cardiac muscle or skeletal muscle, fibrotic degenerative changes in neuronal tissues in the central nervous system as well as the peripheral nervous system, etc.). [S. L. Robbins, R. S. Cotrans, V. Kumar, "Pathologic Basis of Disease", 6th edition, pages 40-84, Saunders, Philadelphia, Pennsylvania (Pub.)].

[0019] With pulmonary interstitial fibrotic hyperplasia, small and firm nodules are palpable throughout the lung tissue, and upon gross examination are recognized from their opaque, airless structure to be foci of abnormal accumulations of fibrotic connective tissue. Such foci vary in size and color according to their age. Their aggressive and continued enlargement and coalescence ultimately leads to collagenous solidification of large segments of the lungs.

[0020] These enlarging foci also impinge upon the lung capillaries thereby to reduce pulmonary blood flow, and at the same time, impede lymphatic drainage from the lungs. As a consequence, exudate accumulates within the alveoli, and secondary thickening of the alveolar wall ensues. These interacting processes sharply reduce the efficiency of the gaseous exchange in the lung alveoli, which is a primary function of the normal lung.

[0021] In addition, these pulmonary fibrotic alternations and accumulations raise the pulmonary blood vessel resistance and lead to cor pulmonale (sharply elevated pulmonary blood pressure). Prolonged elevated pulmonary blood pressure almost invariably leads to congestive heart failure in addition to the cyanosis caused by inadequate pulmonary exchange of oxygen and carbon dioxide. The prognosis is poor and the incidence of severe morbidity and deaths is high.

[0022] Furthermore, the fibrosis of the lung impairs the physiological and biochemical functions of the lung that are independent of the pulmonary gas exchange (oxygen and carbon dioxide) role of the lungs cited above. These Include:

(1) filtration, degradation, and removal of the following substances:

(a) aged leucocytes from the blood, and
(b) particulate matter (for example, tissue cell debris, blood cell aggregates, inert foreign matter, small thrombi); and

(2) synthesis of adequate supplies of heparin.

[0023] Heparin is a useful substance that normally prevents the formation of life-threatening blood clots in the major

blood vessels (for example, cerebral and coronary blood vessels).

C. DIFFERENTIATION BETWEEN ANTI-FIBROTIC ACTIVITY AND ANTI-INFLAMMATORY ACTIVITY

[0024] Pharmacological anti-fibrotic activity as exemplified by the arrest and removal of lung scarring (interstitial hyperplasia and fibrotic foci), or pathologic fibrotic lesions in other organs and tissues described herein, is clearly distinct from and independent of any pharmacological anti-inflammatory activity.

[0025] The debilitating pathologic degeneration of organs and tissues affected by fibrotic disease continues for extended periods of time, measured in months or years, beyond the short-term (hours and days) of exacerbating inflammatory flare-ups (classical clinical and histophathological signs of edema, local heat, and leucocytic infiltration have disappeared).

[0026] The compositions of this invention are effective for treatment of disease caused by the pathologic and excessive fibrotic accumulations such as pulmonary fibrosis, benign prostate hypertrophy, coronary infarcts, cerebral infarcts, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, real fibrotic disease, fibrotic vascular disease (atherosclerosis, varix, or varicose veins), scleroderma, Alzheimer's disease, diabetic retinopathy, glaucoma, etc. The pulmonary fibrosis may have been chemically induced, for example, by the anti-cancer drugs bleomycin or cyclophosphamide or by the weed killer paraquat. The compositions of this invention not only arrest the formation of new fibrotic tissue but causes removal of previously formed fibrotic collagen-containing tissue. These pharmacological properties were heretofore unknown.

[0027] The present invention arrests formation of or causes removal of a pathogenic accumulation of water-insoluble collagenous connective tissue (for example, excessive scar or lesional fibrotic tissue, etc.). By medicinally removing such pathologic collagenous tissue in fibrotic lungs, the invention eliminates or prevents:

(1) the mechanical compression or occlusion (stenosis) of blood vessels (for example, pulmonary arteries, veins, and capillaries), pulmonary bronchioles, and alveoli;
(2) the inhibition of the primary respiratory function of the alveoli of the lungs, namely, the exchange of oxygen and carbon dioxide gases; and
(3) the increased pulmonary blood vessel resistance (cor pulmonale) which readily causes fatal congestive heart failure because of the excessive workload on cardiac muscle that is engendered by the cor pulmonale.

D. TREATMENT WITH PIRFENIDONE (Not part of the invention)

[0028] As is described in the above-referenced EP-A-0 383 591, the dramatic and novel pulmonary anti-fibrotic activity of pirfenidone has been observed and demonstrated in laboratory animal experiments (rats, hamsters, dogs) and in humans. The anti-fibrotic activity in cardiac infarctions, benign prostatic hypertrophy, and post-operative adhesions has been observed in humans. The renal anti-fibrotic activity has-been demonstrated in hamsters. In every instance, the anti-fibrotic activity was clearly distinct from any anti-inflammatory properties.

[0029] The acute toxicity of the ingredient in the medical composition of the present invention which exerts the anti-fibrotic activity is as shown in the table below:

ACUTE TOXICITY (LD : mg/kg)				
Route for Administration				
	p.o. (number)	**i.v. (number)**	**i.p. (number)**	**10% Ointment p.o. (number)**
Animal				
Mouse:	**997.7(40)**	285+/-5(50)	600+/-43(60)	11,500+/-1,100(43)
Rat;				
Male:	**1,295(25)**		430+/-29(42)	**12,500(10)**
Female:	**2,300(30)**			
Guinea Pig:	810+/-25(30)		**460+/-28(25)**	

(continued)

ACUTE TOXICITY (LD : mg/kg)				
Route for Administration				
	p.o. (number)	i.v. (number)	i.p. (number)	10% Ointment p.o. (number)
Animal				
Rabbit:		280+/-32(12)		
Cat:	**500(17)**	**40(4)**		
Dog:	**300(11)**	**200(6)**		
Monkey:		**100(3)**		

[0030] The anti-fibrotic activity measured against pulmonary fibrosis was found to be quite dissimilar to and independent of anti-flammatory activity when these activities were assayed in rats, mice, hamsters, and rabbits. Experiments in dog and human clinical trials affirm these findings. Pirfenidone has been extensively studied for oral anti-fibrotic activity in laboratory animals and in humans. The anti-fibrotic effect in pulmonary fibrosis was demonstrated upon oral administration:

(1) in diets or by gavage to rat or hamsters,
(2) oral capsules in dogs, and
(3) oral administration to humans.

EXAMPLE 1 (not part of the invention)

[0031] The results of a histopathological examination of the lungs of rats for fibrosis (interstitial hyperplasia) after receiving 300mg/kg body weight of pirfenidone in the diet for three months are summarized in Table 2. The individual microscopic readings of the lung are also shown in Table 2, where a score schedule of 0, 1, 2, and 3 reflects the degree of fibrosis.

[0032] The data in Table 2 reveal a statistically significant reduction in the amount of fibrosis in rats receiving pirfenidone as compared to placebo control rats (Group 1). The mean score for the controls (Group 1) was 1.63 +/-0.23, and for Group IV (pirfenidone, 300mg/kg body weight daily was 0.95 +/-0.23.

[0033] Student's T value was 2.43, with P less than 0.02 (highly significant statistically).

[0034] In male and female Beagle dogs, the anti-fibrotic activity was found to be a direct function of the dosage of pirfenidone administered, a classical pharmacological dose-response (Table 3, Figure 1). Lung tissues examined microscopically, and scored on a schedule of 0, 1, 2, and 3 for fibrosis resulted in clear demonstration of statistically significant reduction in pulmonary fibrosis in dogs given the drug as compared to control animals.

[0035] The mean score for Group I (Control) was 2.11 +/-0.31, and for Group IV, which received pirfenidone, 150 mg/kg per day orally in capsules, was 0.22 +/-0.19.

[0036] In hamsters, pulmonary fibrosis induced with crysotile asbestos was removed following oral pirfenidone (Table 4).

[0037] This anti-fibrotic activity was not simply a a palliative (relieving) effect.

[0038] The asbestos-induced fibrosis did not recur after the pirfenidone had been discontinued for two months.

[0039] In mice, pulmonary fibrosis induced with cyclophosphamide was removed following oral administration of pirfenidone and an immunosuppresant drug in humans and is know to produce pulmonary fibrosis in patients as a side effect.

[0040] A similar experience has been observed in trials on human patients with pulmonary fibrosis caused by asbestos.

[0041] For the first time ever, pirfenidone makes possible a pulmonary resolution process whereby a life-threatening solidified fibrotic lung disease can be restored to a relatively normal tissue where the alveoli are no longer collapsed or occluded. That is, the microscopic examination reveals that the tissues are regenerated and become normal, spongy lungs.

[0042] The novel role of pirfenidone in the therapeutic repair of fibrotic lung tissue featuring removal of fibrotic lesions, and concomitant regeneration of normal lung tissue has been observed in experimental asbestosis by histopathological examination of lung tissue specimens under the light microscope, and electron microscopy (Table 4).

[0043] Very little, if any, fibrotic alterations are seen after treatment with adequate doses of pirfenidone.

[0044] A further novel discovery was the demonstration under the electron microscope that the lung cell-imbedded asbestos fibers which had initiated and maintained the extensive fibrotic lesions also had been removed. This was subsequently confirmed by ashing of lung specimens in a laboratory oven, and then determining the asbestos content.

[0045] The discovery of this additional novel "clearing" property of pirfenidone for the first time affords a therapeutic pharmacological remedy for chronic respiratory disease caused by the inhalation and accumulation in the lungs of harmful foreign matter from polluted air, asbestos, industrial dust (grain, lime, fertilizers, cotton fibers, glass fibers, plastics, coal, etc.), resulting in asbestosis, silicosis, and/or black lung of miners, for example.

TABLE 1

CONTRAST BETWEEN PROPERTIES OF COLLAGEN AND ELASTIN			
	Property	Collagen	Elastin
1.	Water soluble	-	+
2.	Converts to gelatin on boiling	+	-
3.	Primarily in white connective tissue	+	-
4.	Primarily in yellow connective tissue	-	+
5.	Primarily associated with highly elastic structure (e.g., blood vessels)	-	+
6.	Primarily in organ structural tissue; fibrotic or scar tissue (e.g., lung fibrosis, etc.)	+	-
7.	Metabolic turnover rate	low	high

TABLE 2

GROUP I (CONTROL)					
		Lung Connective Tissue Score			
Animal Number	**Sex**	**0**	**1**	**2**	**3**
104	F				x
8	M			x	
72	F	x			
74	F				x
75	F		x		
80	F				x
81	F				x
82	F		x		
88	F			x	
94	F		x		
1	M		x		
19	M		x		
26	M			x	
36	M		x		
43	M				x
45	M	x			
52	M		x		
53	M			x	
55	M		x		
	Total:	2	8	4	5
	Mean:	1.63			
	S.E.	0.23			

TABLE 2 (continued)

GROUP IV: PIRFENIDONE, 300 mg/kg (p.o.)					
		Lung Connective Tissue Score			
Animal Number	Sex	0	1	2	3
95	F		x		
86	F				x
93	F		x		
97	F	x			
98	F		x		
99	F		x		
119	F		x		
122	F		x		
123	F	x			
135	F	x			
5	M		x		
11	M		x		
16	M		x		
29	M	x			
31	M	x			
32	M		x		
34	M		x		
35	M			x	
40	M			x	
	Total:	5	11	2	1
	Mean:	0.95			
	S.E.:	0.18			
	t:	2.43			
	P:	<0.02			

TABLE 3

EFFECT OF ORAL PIRFENIDONE UPON PULMONARY INTERSTITIAL HYPERPLASIA (FIBROSIS) IN DOGS							
Group	Number of Dogs	Hyperplasia Scores*				Average Scores	Incidence of Normal Lung
		0	1	2	3		
I. Control (0.0%)	**9**	**0**	**3**	**2**	**4**	2.11+/-0.31	**0/9**
II. Pirfenidone (16.7%) 25 mg/kg/day	**6**	**1**	**1**	**4**	**0**	1.50+/-0.34	**1/6**
III. Pirfenidone (25.0%) 75 mg/kg/day	**8**	**2**	**2**	**3**	**1**	1.38+/-0.38	**2/8**

* Degree of Hyperplasia (fibrosis)
0 = normal tissue
1 = minimal
2 = moderate
3 = severe

TABLE 3 (continued)

EFFECT OF ORAL PIRFENIDONE UPON PULMONARY INTERSTITIAL HYPERPLASIA (FIBROSIS) IN DOGS							
Group	**Number of Dogs**	**Hyperplasia Scores***				**Average Scores**	**Incidence of Normal Lung**
		0	**1**	**2**	**3**		
IV. Pirfenidone 150 mg/kg/day	**9**	**7**	**2**	**0**	**0**	0.22+/-0.15**	**7/9**

* Degree of Hyperplasia (fibrosis)
0 = normal tissue
1 = minimal
2 = moderate
3 = severe

** Highly Statistically Significant (P<0.001)

TABLE 4

EFFECT OF ORAL PIRFENIDONE UPON ASBESTOS-INDUCED PULMONARY INTERSTITIAL FIBROSIS IN HAMSTERS

Group	Animal Number	Lung Density	Pulmonary Fibrosis Score Light Microscope	Pulmonary Fibrosis Score Electron Microscope
I. Control No Asbestos (-); No Pirfenidone	1	0.95	0	0
	2	0.90	1	0
	3	1.05	1	1
	4	1.10	0	0
Average		1.00+/-0.05	0.50+/-0.25	0.25+/-0.25
II. Asbestos (+); No Pirfenidone (-)	5	2.70	3	3
	6	1.90	2	3
	7	2.53	3	2
	9	2.98	3	3
Average		2.53+/-0.23	2.75+/-0.25	2.75+/-0.25
III. Asbestos (+)*; Plus Pirfenidone (+)	10	0.98	0	0
	12	1.04	2	1
	13	1.26	1	0
	14	1.41	1	0
Average		1.17+/-0.10	1.00+/-0.41	0.25+/-0.25
Student's "T" Values:				
Group II vs. Group III:		5.9**	3.7**	7.1**
Group II vs. Group I:		6.5**	5.9**	7.1**

Degree of Fibrosis:
0 = normal tissue
1 = minimal
2 = moderate
3 = severe

* Asbestos by inhalation for 5 days; Pirfenidone, 500 mg/kg/day, orally in the diet for two months, beginning two months after the five-day exposure to asbestos dust.
** Highly Statistically Significant (P<0.001).

TABLE 5

EFFECT OF ORAL PIRFENIDONE UPON CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL FIBROSIS IN MICE				
NO. Mice	Lung Dry Wt. Mg.	Lung OH- Proline MicGm/Lung	Lung OH- Proline MicGm/Mg	Lung FIBROSIS Scores## (N/N)
GROUP I-A (cyclophosphamide only, 200 mg/kg, i.p.)				
10	50.0+/-1.3	313+/-10	6.01+/-.24	4.43+/-43 (0/5)
GROUP I-B (cyclophosphamide only, 200 mg/kg, i.p.)				

Scoring (0 through 6) of lung interstitial hyperplasia and fibrotic nodule formation based on technique recommended by the Pneumoconiosis Committee of the College of American Pathologists, and the National Institute for Occupational Safety and Health (Ref: Arch. Path. Lab. Med., vol. 106,1982).

TABLE 5 (continued)

EFFECT OF ORAL PIRFENIDONE UPON CYCLOPHOSPHAMIDE-INDUCED INTERSTITIAL FIBROSIS IN MICE				
NO. Mice	**Lung Dry Wt. Mg.**	**Lung OH- Proline MicGm/Lung**	**Lung OH- Proline MicGm/Mg**	**Lung FIBROSIS Scores## (N/N)**
8	46.8+/-2.3	406+/-21	8.85+/-0.58	3.90+/-0.23 (0/5)
COMBINED GROUPS I-A AND I-B (cyclophosphamide only, 200 mg/kg, i.p.)				
18	48.9+/-1.3	360+/-18	7.50+/-0.44	4.34+/-0.26(0/10)
GROUP II (cyclophosphamide, 200 mg/kg, i.p., plus pirfenidone, 500 mg/kg/day, p.o.)				
10	52.4+/-0.9	284+/-13**	5.46+/-0.31**	2.99+/-0.75(3/5)*
GROUP III (saline control; no cyclophosphamide; no pirfenidone)				
6	45.3+/-1.2	317+/-20	7.00+/-0.42	0.26+/-0.15(5/5)#
GROUP IV (pirfenidone, 500 mg/kg/day, p.o.; saline; no cyclophosphamide)				
6	39.0+/-2.8**	288+/-9**	7.60+/-0.60	0.68+/-0.35** **(5/5)#**

** Differs significantly (P <0.01) from Combined Groups I-A and I-B (Student T test for differences between means).

Differs significantly (P <0.05) from Combined Groups I-A and I-B (Chi-square two-fold contingency table; incidence of scores 3.0 or less).

Scoring (0 through 6) of lung interstitial hyperplasia and fibrotic nodule formation based on technique recommended by the Pneumoconiosis Committee of the College of American Pathologists, and the National Institute for Occupational Safety and Health (Ref: Arch. Path. Lab. Med., vol. 106,1982).

[0046] Clinical human open trials have been undertaken as follows:

1. Pulmonary fibrosis diagnosed as caused by asbestos was treated with pirfenidone and closely and objectively followed in two subjects. Clinical impressions were dramatic and highly favorable.
2. Pulmonary fibrosis diagnosed as idiopathic in nature was treated with pirfenidone and closely and objectively followed in one subject for over two years. Clinical impressions were highly favorable.
3. Benign prostate hypertrophy in three elderly subjects (66-100 years) was treated with pirfenidone with very good to excellent clinical results. Two subjects suffered from frequency, severe nocturia, incontinence, constant urgency, and in the third these symptoms were less severe. Clinically, all had enlarged prostates that explained the symptoms. The results were dramatic in the eldest subject within two weeks of therapy. Nocturia of 6-7 trips (every 60-90 minutes) per night was reduced to 1 or 2 nightly (4-5 hours apart). In the other two patients, nocturia 3-4 times (every 2-3 hours) was reduced to once nightly 4-5 hours after retiring. In all cases digital examination of the prostate revealed a detectable reduction in the size of the prostate in 3-4 weeks.
4. Fibrosis of the ventricular myocardium, an outcome of repeated coronary infarcts was treated with pirfenidone in one subject (diagnosed as terminal), with objective evidence of the reduction of the fibrosis (electrocardiogram maps and nuclear resonance determinations). The subject lived for an additional three years, despite the fact that the administration of the drug was terminated after 18 months, due to a limited supply.
5. Inhibition of excessive scar formation by direct application of pirfenidone ointment to skin lesions in 10 cases. Mild to moderate skin laceration or lesions failed to generate skin scars, or caused only minimal scarring when pirfenidone ointment was directly applied to the lesion.

[0047] Examples of medical preparations include: (1) capsules, (2) tablets, (3) powders, (4) granules, (5) syrups, (6) injection (intravenous, intramuscular, or drip administration), (7) cream, (8) ointment, (9) inhalation, (10) eye drop, (11) suppositories, (12) pills, etc.

[0048] The above preparations are available. Among them, capsules, injections, cream, and ointments are preferred preparations.

[0049] Preferably, the N-substitued 2-(1H) pyridones according to the invention are adminstered in an amount of from 25mg to 9600mg per day, more preferably at a level of from 75 mg to 9600 mg per day. Conveniently they can be administered in an amount of from 25 mg to 3200 mg contained in a capsule.

TEST EXAMPLE 1 (No longer part of the invention)

[0050] In one capsule, 800 mg, 1200 mg, or 1600 mg of pirfenidone is contained.

TEST EXAMPLE 2 (No longer part of the invention)

[0051] Hydrophilic ointment containing 5 to 10% pirfenidone.

[0052] The average oral dosage for anti-fibrotic activity in humans is 3600 milligrams per day, with a range of from about 2400 milligrams to about 4800 milligrams per day. Administration may be in divided dosage - for example, 1200 milligrams three times per day.

E. COMPOSITIONS AND DOSAGES FOR THE PRESENT INVENTION

[0053] The above-referenced US Patent No. 3,839,346 describes methods of preparation of some N-substituted 2-(1H)-pyridones useful in the present invention. Those pyridones are:

3-Methyl-1-phenyl-2-(1H) pyridone
6-Methyl-1-phenyl-2-(1H) pyridone
3,6-Dimethyl-1-phenyl-2-(1H) pyridone
5-Ethyl-1-phenyl-2-(1H) pyridone
1-Phenyl-2-(1H) pyridone
1,3-Diphenyl-5-methyl-2-(1H) pyridone

[0054] Effective dosages and rates of application of the compositions of the present invention have been found to be effective, or can be expected to be effective, in a range of from about one-quarter to about twice the dosages given above for pirfenidone.

[0055] The compositions of the present invention may be administered in forms consisting of capsules, tablets, powders, granules, syrups, injectable fluids, pills, creams, ointments, inhalable fluids, eye drops, and suppositories.

Claims

1. The use of a compound selected from 3-methyl-1-phenyl-2-(1H)-pyridone, 6-methyl-1-phenyl-2-(1H) pyridone, 3,6-dimethyl-1-phenyl-2-(IH) pyridone, 5-ethyl-1-phenyl-2-(1H) pyridone, 1-phenyl-2-(1H)-pyridone and 1,3-diphenyl-5-methyl-2-(1H)-pyridone in the preparation of a medicament for the reparation and prevention of fibrotic lesional tissue in a mammal.

2. The use according to claim 1, in which the compound is administered at a dosage from about 5 to 300 mg per kilogram of body weight per day.

3. The use according to claim 1, in which said compound is present in said medicament in an amount from 25 mg to 3200 mg.

4. The use according to claim 3, in which said compound is present in said medicament in an amount from 200 mg to 3200 mg.

5. The use according to any preceding claim, in which said fibrotic lesional tissue is associated with a condition in the group consisting of pulmonary fibrosis, benign prostate hypertrophy, coronary infarcts, cerebral infarcts, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, sceleroderma, Alzheimer's disease, diabetic retinopathy, and skin lesions.

6. The use according to any preceding claim, in which said medicament is in the form of capsules, tablets, powders, granules, syrups, injectable fluids, and pills.

7. The use according to claim 1, in which the medicament is for topical administration and contains said compound in a concentration from 1 to 20% by weight.

8. The use according to claim 7, in which said fibrotic lesional tissue is associated with a condition in the group

consisting of musculoskelet fibrosis, post-surgical adhesions, scleroderma, glaucoma, and skin lesions.

9. The use according to claim 7 or claim 8, in which said medicament is in the form of creams, ointments, hydrophilic ointments, inhalable fluids, eye drops, and suppositories.

10. The use according to any preceding claim, in which the compound is 5-ethyl-1-phenyl-2-(1H) pyridone.

Patentansprüche

1. Verwendung einer unter 3-Methyl-1-phenyl-2-(1H)-pyridon, 6-Methyl-1-phenyl-2-(1H)pyridon, 3,6-Dimethyl-1-phenyl-2-(1H)-pyridon, 5-Ethyl-1-phenyl-2-(1H)-pyridon, 1-Pheny-2-(1H)-pyridon und 1,3-Diphenyl-5-methyl-2-(1H)-pyridon ausgewählten Verbindung bei der Zubereitung eines Medikamentes zur Reparatur und Vorbeugung fibriotisch geschädigten Gewebes bei einem Säugetier.

2. Verwendung gemäß Anspruch 1, wobei die Verbindung in einer Dosis von etwa 5 bis 300 mg pro Kilogramm Körpergewicht und Tag verabreicht wird.

3. Verwendung gemäß Anspruch 1, wobei die besagte Verbindung in dem besagten Medikament in einer Menge von 25 mg bis 3200 mg vorhanden ist.

4. Verwendung gemäß Anspruch 3, wobei die besagte Verbindung in dem besagten Medikament in einer Menge von 200 bis 3200 mg vorhanden ist.

5. Verwendung gemäß einem der vorherigen Ansprüche, wobei das besagte fibriotisch geschädigte Gewebe mit einem Zustand aus der Gruppe verbunden ist, die aus Lungenfibriose, gutartiger Prostatahypertrophie, Herzinfarkten, Hirninfarkten, myocardialen Fibriosen, Muskel-Skelett-Fibriosen, post-operativen Adhesionen, Leberzirrhosen, Nieren-Fibrioseerkrankungen, fibriotisehen Gefäßerkrankungen, Skeleroderma, Alzheimerkrankheit, diabetischer Retinopathie und Hautläsionen besteht.

6. Verwendung gemäß einem der vorherigen Ansprüche, wobei das besagte Medikament die Form von Kapseln, Tabletten, Pulvern, Granulaten, Sirups, injizierbaren Flüssigkeiten und Pillen hat.

7. Verwendung gemäß Anspruch 1, wobei das besagte Medikament zur äußerlichen Anwendung ist und die besagte Verbindung in einer Konzentration von 1 bis 20 Gew.-% enthält.

8. Verwendung gemäß Anspruch 7, wobei das besagte fibriotisch geschädigte Gewebe mit einem Zustand aus der Gruppe verbunden ist, die aus Muskel-Skelett-Fibriosen, post-operativen Adhesionen, Skeleroderma, Glaucom und Hautläsionen besteht.

9. Verwendung gemäß Anspruch 7 oder 8, wobei das besagte Medikament die Form von Cremes, Salben, hydrophilen Salben, inhalierbaren Fluiden, Augentropfen und Suppositorien hat.

10. Verwendung gemäß irgendeinem der vorherigen Ansprüche, wobei die Verbindung 5-Ethyl-1-phenyl-2-(1H)-pyridon ist.

Revendications

1. Utilisation d'un composé choisi parmi la 3-méthyl-1-phényl-2-(1H)-pyridone, la 6-méthyl-1-phényl-2-(1H)-pyridone, la 3,6-diméthyl-1-phényl-2-(1H)-pyridone, la 5-éthyl-1-phényl-2-(1H)-pyridone, la 1-phényl-2-(1H)-pyridone et la 1,3-diphényl-5-méthyl-2-(1H)-pyridone dans la préparation d'un médicament destiné à la réparation et à la prévention des lésions tissulaires de type fibrose chez un mammifère.

2. Utilisation selon la revendication 1, dans laquelle le composé est administré à une dose d'environ 5 à 300 mg par kilogramme de poids corporel par jour.

3. Utilisation selon la revendication 1, dans laquelle ledit composé est présent dans ledit médicament en quantité de

25 mg à 3200 mg.

4. Utilisation selon la revendication 3, dans laquelle ledit composé est présent dans ledit médicament en quantité de 200 mg à 3200 mg.

5. Utilisation selon l'une quelconque des revendications précédente, dans laquelle ladite lésion tissulaire de type fibrose est associée à état pathologique parmi le groupe constitué par les fibroses pulmonaires, l'hypertrophie bénigne de la prostate, l'infarctus coronarien, l'infarctus cérébral, les fibroses myocardiaques, les fibroses musculosquelettiques, les adhérences post-chirurgicales, la cirrhose du foie, les fibroses rénales, les fibroses vasculaires, les sclérodermies, la maladie d'Alzheimer, la rétinopathie diabétique et les lésions de la peau.

6. Utilisation selon l'une quelconque des revendications précédente, dans laquelle ledit médicament est sous la forme de gélules, comprimés, poudres, granulés, sirops, fluides injectables et pilules.

7. Utilisation selon la revendication 1, dans laquelle le médicament est destiné à une administration locale et contient ledit composé à une concentration de 1 à 20% en poids.

8. Utilisation selon la revendication 7, dans laquelle ladite lésion tissulaire de type fibrose est associée à un état pathologique parmi le groupe constitué par les fibroses musculosquelettiques, les adhérences post-chirurgicales, les sclérodermies, les glaucomes et les lésions de la peau.

9. Utilisation selon la revendication 7 ou la revendication 8, dans laquelle ledit médicament est sous la forme de crèmes, de pommades, de pommades hydrophiles, de fluides pour inhalation, de gouttes oculaires et de suppositoires.

10. Utilisation selon l'une quelconque des revendications précédente, dans laquelle le composé est la 5-éthyl-1-phényl-2-(1H)-pyridone.

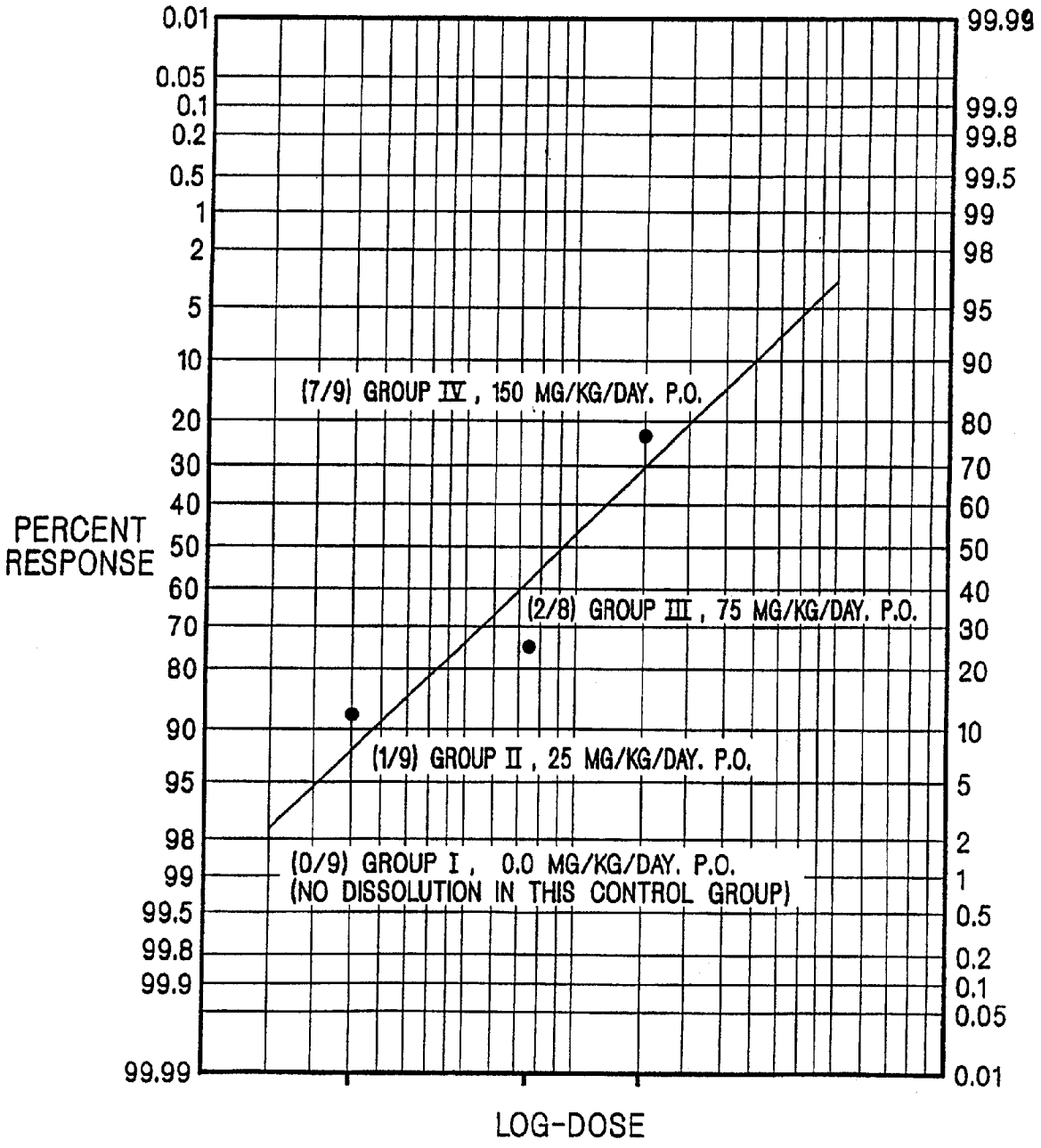
PERCENT RESPONSE
0.01
0.05
0.1
0.2
0.5
1
2
5
10
20
30
40
50
60
70
80
90
95
98
99
99.5
99.8
99.9
99.99
99.99
99.9
99.8
99.5
99
98
95
90
80
70
60
50
40
30
20
10
5
2
1
0.5
0.2
0.1
0.05
0.01
(7/9) GROUP IV , 150 MG/KG/DAY. P.O.
(2/8) GROUP III , 75 MG/KG/DAY. P.O.
(1/9) GROUP II , 25 MG/KG/DAY. P.O.
(0/9) GROUP I , 0.0 MG/KG/DAY. P.O.
(NO DISSOLUTION IN THIS CONTROL GROUP)
LOG-DOSE

FIG. 1